

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Mark Tawa, et al.	Confirmation No.:	4554
Application No.:	10/541,216	Group Art Unit:	1627
Filing Date:	June 29, 2005	Examiner:	Claytor, D.R.
For:	PHARMACEUTICAL COMPOSITIONS WITH IMPROVED DISSOLUTIONS		

DECLARATION UNDER 37 C.F.R. § 1.132

I, Mark Tawa, a named inventor in the above-identified patent application declare that:

1. I have read and understand the rejection of claims 46-68 under 35 U.S.C. § 102 in the December 23, 2010 final Office Action. In particular, I understand that claims 46-48 are rejected as being anticipated by Remenar et al. (U.S. Published Application No. 20060052432).
2. I understand that the Examiner asserts that:
 - a. Remenar et al. claims priority to U.S. Application Serial No. 60/427,086, which was filed on November 15, 2002;
 - b. U.S. Application Serial No. 60/427,086 discloses a sodium salt form of celecoxib.
 - c. U.S. Application Serial No. 60/427,086 discloses that a poloxamer can act as a precipitation retardant.
 - d. Priority for Remenar et al. goes to at least November 15, 2002.

(See final Office Action at page 2).
3. I and my co-inventors were in possession of the invention claimed in the above-identified patent application prior to November 15, 2002, the earliest filing date for Remenar et al. This is evidenced by the contents of the attached laboratory notebook pages.
4. The dates on each of the laboratory notebook pages, which have been redacted, were all prior to November 15, 2002.

5. The laboratory notebook pages demonstrate that I and my co-inventors were in possession of the invention recited in claims 46-68 prior to the November 15, 2002 filing date. More particularly, the laboratory notebook pages demonstrate that I and my co-inventors prepared:

A pharmaceutical composition comprising a salt form of celecoxib and a poloxamer.
(See Laboratory Notebook No. 129, Pages 14-18).

A pharmaceutical composition comprising a salt form of celecoxib and an enhancer
(e.g., hydroxypropylcellulose and hydroxypropylmethylcellulose). Laboratory
Notebook No. 114, Pages 100-102

The declarant further states that the above statements were made with the knowledge that willful false statements and the like are punishable by fine and/or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful false statement may jeopardize the validity of the above-identified patent application or any patent resulting therefrom.

Date: 16 March 2011

Mark Tawa
(Signature of Mark Tawa)

Attachments:

Laboratory Notebook No. 129, Pages 14-18
Laboratory Notebook No. 114, Pages 100-102

NOTEBOOK NO. 114
ISSUED TO Mark Tawa
ON 7/1/02
DEPARTMENT Solid state Chemistry
RETURNED



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TITLE Celecoxib Na + Vit E TAPS MixturesBook No. 114

From Page No. _____

Celecoxib Na - MT-114-94-A

Vitamin E TAPS - Eastman Lot 90001000

Poloxamer 237 - Spectrum Lot PE0487

Hydroxypropyl cellulose 100,000 - Alfa Aesar Lot L02548

Hydroxypropyl methylcellulose (80-120 cps) - Aldrich Lot 107684U

" (15,000 cps) - Aldrich Lot 0192966

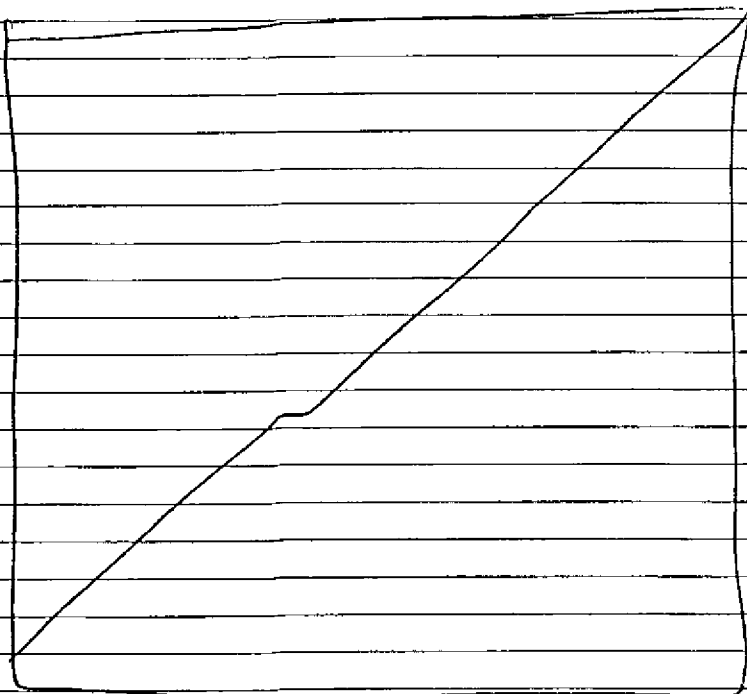
Avicel (microcrystalline cellulose) PH 200 - FMC Lot 100366

1) Vitamin E TAPS - 103.15 mg
 HPC - 99.59 mg
 Celecoxib Na - 112.4 mg

2) Vitamin E TAPS - 100.34
 HPMC (80-120) - 99.96
 Celecoxib Na - 110.7

3) Vitamin E TAPS - 103.72
 HPMC (15,000) - 99.76
 Celecoxib Na - 111.3

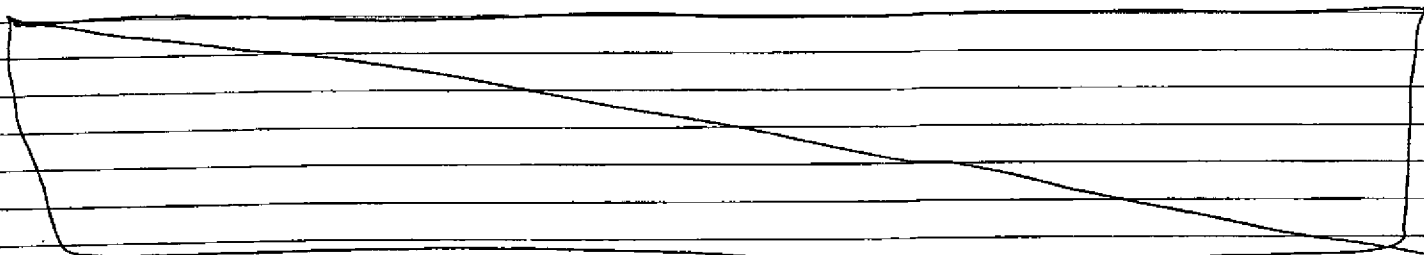
4) Vitamin E TAPS - 102.19
 Avicel (PH 200) - 101.34
 Celecoxib Na - 110.8



- mixtures 1-4 were made via heating of Vitamin E TAPS to melt it (by heat gun); Celecoxib Na added and mixed together followed by 3rd excipient

- all steps included stirring

- mixtures were cooled and weighed out for dissolution assays

To Page No. 101

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Lisa A. S. Papp

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TITLE Col Na + vit E TOPS Mixtures (cont)

Book No. 14From Page No. 100

Assay Vial 1 (95.4 mg)		Assay Vial 2 (94.2 mg)	
HPLC Vial	time	HPLC Vial	time
9	1:01	15	1:00
10	3:00	16	3:00
11	5:00	17	5:05
12	20:02	18	10:01
13	20:12	19	20:00
14	30:00	20	30:00

- still hasn't completely
broken up yet @ 30 min

~~large~~ ^{small} chunk not dissolved w/ ligated @ 30 min

Assay Vial 3 (94.3 mg)

Assay Vial 4 (93.5 mg)

HPLC Vial	time	HPLC Vial	time
21	1:00	27	1:00
22	3:18	28	3:05
23	5:00	29	5:10
24	10:02	30	10:11
25	20:00	31	20:00
→ 26	30:00	32	30:00

Shook

- large clump stays
undissolved

... did disperse throughout
mixture

- all assays run w/ 15 mL of SGF (Zhang Zhang)

- 0.75 mL aliquots removed and filtered through 0.2 µm PVDF syringe filters

- the first ~ 0.6 mL are discarded and the remaining filtrate is collected

- from the filtrate is collected and 0.5 mL which is quenched w/
0.70 mL of MeOH (15x dilution)

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TITLE HPLC data for p 100-101Book No. 114From Page No. 101*Mark Tawa*

ATTR0230.xls

data

Transform Pharmaceuticals				
Analytical Testing Data				
ATR/R #:	230			
HPLC sample	Name	Time Point	Dilution Factor	Conc mg/mL
1	1:1 Vit E TGPS: CelNa Content uniformity		1	0.091
2	1:1 Vit E TGPS: CelNa Content uniformity		1	0.123
3	1:1 Vit E TGPS: CelNa Content uniformity		1	0.068
4	1:1 Vit E TGPS: CelNa Content uniformity		1	0.072
5	1:1 Vit E TGPS: Cel Content uniformity		1	0.112
6	1:1 Vit E TGPS: Cel Content uniformity		1	0.096
7	1:1 Vit E TGPS: Cel Content uniformity		1	0.137
8	1:1 Vit E TGPS: Cel Content uniformity		1	0.110
9	1:1:1 Vit E TGPS: HPC: CelNa (2 mg/ml API)	1 min	15	0.073
10	1:1:1 Vit E TGPS: HPC: CelNa (2 mg/ml API)	3 min	15	0.200
11	1:1:1 Vit E TGPS: HPC: CelNa (2 mg/ml API)	5 min	15	0.449
12	1:1:1 Vit E TGPS: HPC: CelNa (2 mg/ml API)	10 min	15	0.798
13	1:1:1 Vit E TGPS: HPC: CelNa (2 mg/ml API)	20 min	15	1.254
14	1:1:1 Vit E TGPS: HPC: CelNa (2 mg/ml API)	30 min	15	1.520
15	1:1:1 Vit E TGPS: lv HPMC: CelNa (2 mg/ml API)	1 min	15	0.011
16	1:1:1 Vit E TGPS: lv HPMC: CelNa (2 mg/ml API)	3 min	15	0.196
17	1:1:1 Vit E TGPS: lv HPMC: CelNa (2 mg/ml API)	5 min	15	0.381
18	1:1:1 Vit E TGPS: lv HPMC: CelNa (2 mg/ml API)	10 min	15	0.672
19	1:1:1 Vit E TGPS: lv HPMC: CelNa (2 mg/ml API)	20 min	15	1.202
20	1:1:1 Vit E TGPS: lv HPMC: CelNa (2 mg/ml API)	30 min	15	1.186
21	1:1:1 Vit E TGPS: hv HPMC: CelNa (2 mg/ml API)	1 min	15	0.004
22	1:1:1 Vit E TGPS: hv HPMC: CelNa (2 mg/ml API)	3 min	15	0.018
23	1:1:1 Vit E TGPS: hv HPMC: CelNa (2 mg/ml API)	5 min	15	0.006
24	1:1:1 Vit E TGPS: hv HPMC: CelNa (2 mg/ml API)	10 min	15	0.003
25	1:1:1 Vit E TGPS: hv HPMC: CelNa (2 mg/ml API)	20 min	15	0.003
26	1:1:1 Vit E TGPS: hv HPMC: CelNa (2 mg/ml API)	30 min	15	0.012
27	1:1:1 Vit E TGPS: Avicel PH 200: CelNa (2 mg/ml API)	1 min	15	0.298
28	1:1:1 Vit E TGPS: Avicel PH 200: CelNa (2 mg/ml API)	3 min	15	0.715
29	1:1:1 Vit E TGPS: Avicel PH 200: CelNa (2 mg/ml API)	5 min	15	0.617
30	1:1:1 Vit E TGPS: Avicel PH 200: CelNa (2 mg/ml API)	10 min	15	0.190
31	1:1:1 Vit E TGPS: Avicel PH 200: CelNa (2 mg/ml API)	20 min	15	0.137
32	1:1:1 Vit E TGPS: Avicel PH 200: CelNa (2 mg/ml API)	30 min	15	0.127

Mark Tawa

- good solubility profiles seen for HPC and HPMC (low viscosity)

- going to carry forward w/ one of these two formulations

To Page No.

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Lisa A. Coppetello

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DEPARTMENT Solid-State Chemistry
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From Page No. _____

Goal: Test various solid-state ratios of Poloxamer in the solid state w/ TPI-336 Na. Measure dissolution properties

Design:

Excipient: ① Poloxamer 237 - Spectrum # P1167, Lot # PEO487, ② Poloxamer 407 - Spectrum P1166, Lot # QP0478

③ Poloxamer 338 spectrum P1172, Lot # PH0500

④ PVP K30 - spectrum P1454, Lot # L02180

SGF: pH 1.7 adjusted - diluted 5x - 15 ml volume per sample for 2 mg API / ml dose
MT-114.81A

Assay #	Grind	Excipient / mg	Ratio	API (mg)	#	Assay Vial (mg)	Grind Type
1		Poloxamer 237/81.7	2:1	46.5	1	#1, 95.2	clump, slight graying
2		Poloxamer 237/81.2	1:1	79.6		#2, 65.5 #3, 65.5	loose powder
3		Poloxamer 237/162.6	2:1	92.4		#4, 153.8 #5, 153.7	powder
		PVP / 162.6	2:1	—			
4		Poloxamer 338/181.3	2:1	93.5		#6, 63.4 #7, 61.5	powder
		Poloxamer 407/81.3	1:1	94		#8, 65.5	
5		Poloxamer 407/81.3	1:1	94		#9, 64.8	powder
6		Poloxamer 188/6.8	1:1	Returned by P.C.R.			powder

Note: Some samples were performed and ground by Mark Tawar, ZT or P.C.R. For the samples shown below are samples were filtered by Hector Green using a 0.2 um PVDF filter.

Assay Vial #1	Assay Vial #2	Assay Vial #3	Assay Vial #4
Time HPLC #	Time HPLC #	Time HPLC #	Time HPLC #
40 1	41 6	57 11	0:42 16
1:35 2	1:49 7	1:45 12	1:30 18
3:00 3	2:53 8	2:57 13	2:58 17
4:57 4	4:58 9	4:55 14	4:59 19
10:00 5	10:00 10	9:54 15	9:56 23

Assay Vial #7	Assay Vial #8	Assay Vial #9
Time HPLC #	Time HPLC #	Time HPLC #
0:46 20	0:44 25	0:37 30
1:29 21	1:28 26	1:31 31
2:57 22	2:56 27	3:00 32
4:56 24	4:08 29	4:59 34
9:55 28	9:58 33	9:59 35

For sample collection, the sample procedure shown in page 8, items ② - ⑤ were followed.

extra notes: 20 ml scintillation vials were used and small stir bars were used.

The data from HPLC is stored under filename ATPL0209. Page No. _____

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Jami Cling.

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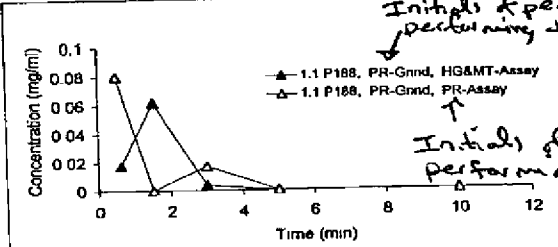
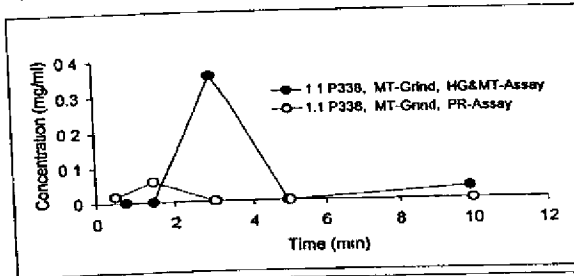
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Book No. _____

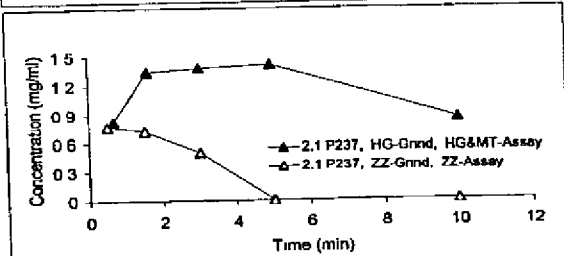
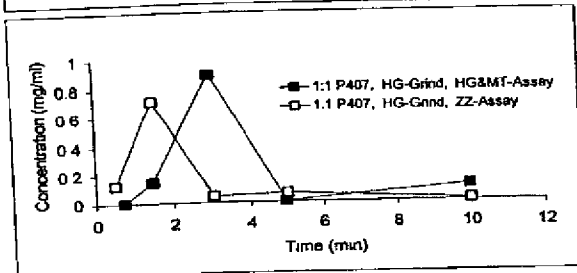
From Page No. H

Replicate assay performed using different 1) researchers, and 2) sized stir bars

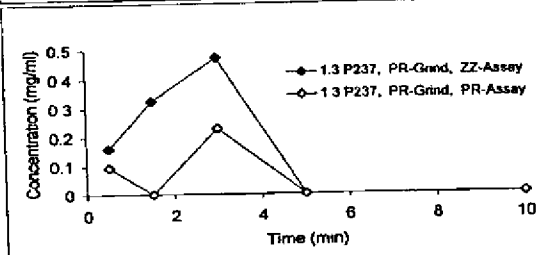
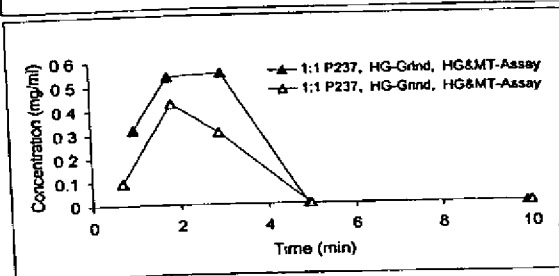
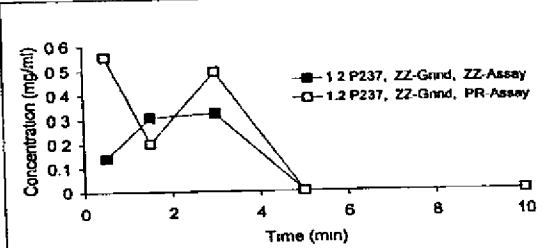
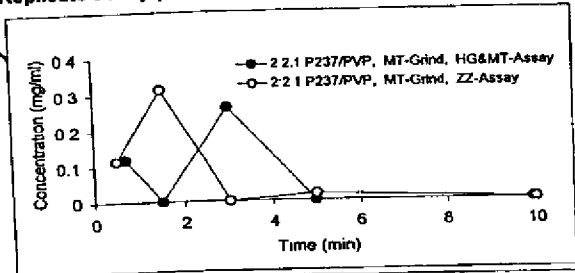


Initials of person performing the grind

Initials of person(s) performing the assay



Replicate assay performed using same size stir bars; researcher may vary



Comments: In general the dataset was very inconsistent among the replicates. Possible reasons are the following:

- ① Inconsistent grinds.
- ② Different stir bars were used.

- when different sized stir bars were used (ZZ and PR used large stir bars; MT + HG used small) a shift in the maximum conc. was observed.
- when the same stir bar was used, no shift was observed among the replicates

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Jamie O'G.

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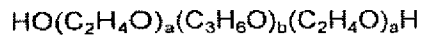
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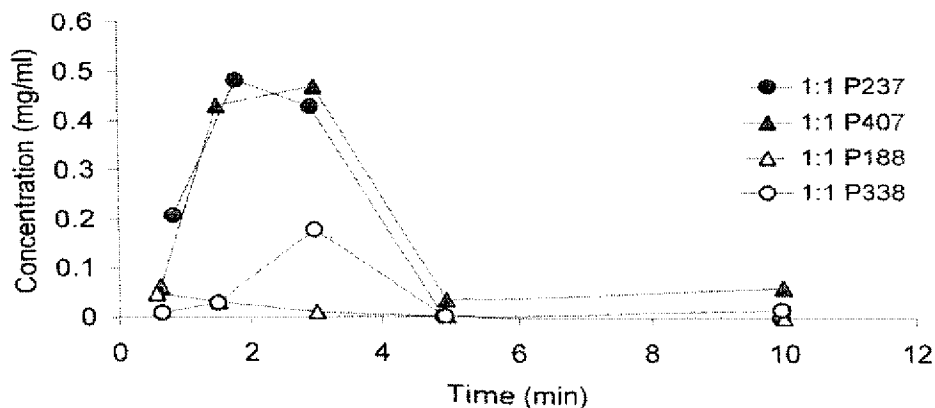
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Poloxamer	Physical form	a	b	Average molecular weight	Percent a	Percent b	Ratio a/b
124	Liquid	12	20	2090-2360	0.38	0.63	0.60
188	Solid	80	27	7680-9510	0.75	0.25	2.96
		64	37	6840-8830			1.73
338	Solid	141	44	12 700-17 400	0.76	0.24	3.20
		101	56	9840-14 600			1.80



Qualitative effect of poloxamer a/b ratio



Notes:

1. Average dataset between two replicate measurements
2. Shift effect with respect to time (i.e., maximum conc.) have been ignored.

For further analysis, Poloxamers having similar percent A and percent B concentration were compared against other poloxamers. This data represents repeated data shown in page 15 that was averaged. Because of the previously observed shifts, only qualitative information can be extracted from this figure. As shown, it seems that higher % B and lower percent A results in higher concentrations of TP1336 Na over time.

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TITLE TPI-336Na Dissolution Study

Book No. _____

From Page No. _____

Goal: Test effect of grind API/excipient and stirring bar size on dissolution of TPI-336Na

Design

Excipient: ① Poloxamer 237 - Spectrum #P1167, PEO-237

API Dose 2mg/mL TPI-336Na - MT-114-89A

SGF adjusted pH 1.7, diluted 5x with DI H₂OMethods

Three API Mixtures

① Mixture 3 - Heavy Grind

- Pre-Grind Poloxamer 237 to fine particle size (i.e., 1 min) - 40.1 mg
- Add TPI-336Na - 92 mg
- Grind for 10 min
- Dispense into Assay Vials 7+8

② Mixture 2 - Light Grind

- Pre-grind Poloxamer 237 to fine particle size (i.e., 1 min) - 100.1 mg
- Add TPI-336Na - 231.5 mg
- Dispense into Assay vials 3-6

③ Mixture 1 - made by Mark Taylor - Notebook #114, page 90. (No Grind)

- Same Ratio

- Dispense into assay vials 1-2.

Table of Assay Vials

Assay Vial	Weight(mg)	Vol (mL)	Grind	Appearance	Stir Bar
1	50	15	None	Loose Powder	small
2	50.5	15	None		small
3	48.1	14.5	Light		small
4	48.7	14.7	Light		small
5	47.3	14.7	Light		large
6	48.8	14.7	Light		large
7	46.3	14.0	Heavy	Chunky	small
8	45.7	13.8	Heavy	Chunky	small

Assay Vial #1		Assay Vial #2		Assay Vial #3		Assay Vial #4	
Time	HPLC #	Time	HPLC #	Time	HPLC #	Time	HPLC #
0:45	1-1	3:38	2-1	3:32	3-1	2:27	4-1
1:55	1-2	1:45	2-2	1:14	3-2	1:25	4-2
2:53	1-3	2:44	2-3	2:24	3-3	2:36	4-3
3:40	1-4	3:45	2-4	3:10	3-4	3:43	4-4
4:56	1-5	4:54	2-5	4:28	3-5	4:55	4-5
9:59	1-6	10:01	2-6	9:59	3-6	9:52	4-6

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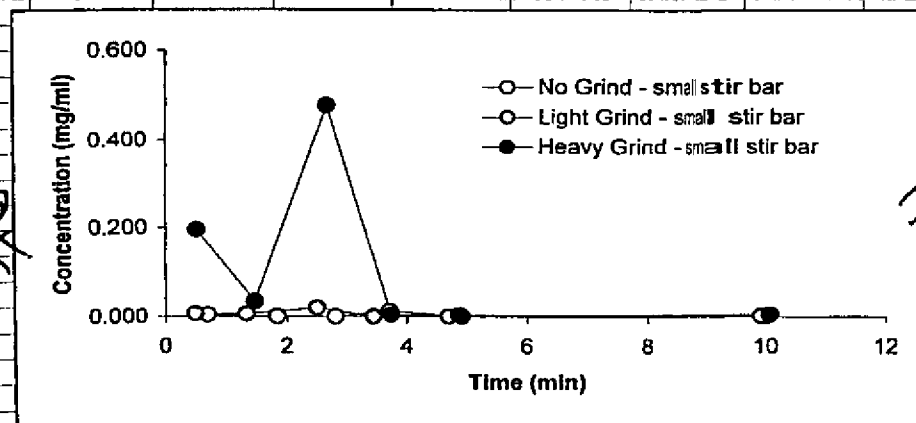
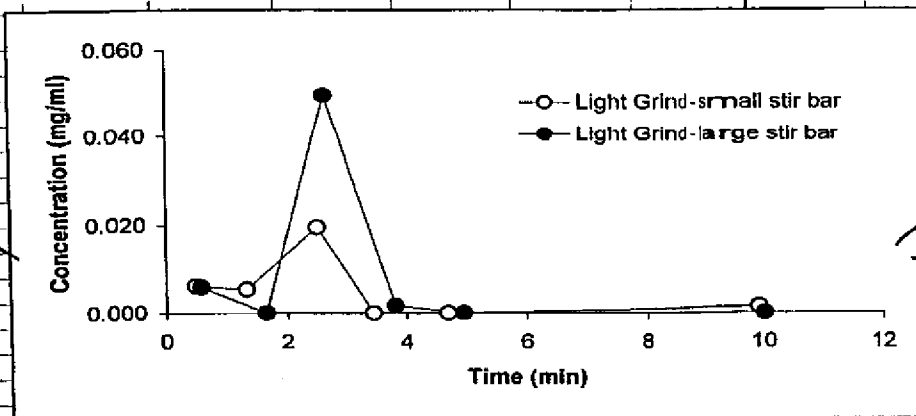
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jeannie cheng


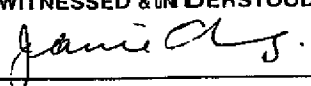
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Assay Vial #5		Assay Vial #6		Assay Vial #7		Assay Vial #8	
Time	HPLC #	Time	HPLC #	Time	HPLC #	Time	HPLC #
27	5-1	42	6-1	33	7-1 cloud	28	8-1
1:29	5-2	1:49	6-2	1:32	7-2 little	1:24	8-2
2:29	5-3	2:45	6-3	2:42	7-3 cloudy	2:36	8-3
3:40	5-4	3:57	6-4	3:35	7-4 clear	3:53	8-4
4:54	5-5	5:00	6-5	4:47	7-5 clear	4:59	8-5
10:00	5-6	10:02	6-6	10:08	7-6	10:01	8-6



Saved in file: ATRO210.xls in user/Hector/Programs/P2P1
TPI-336 / ATRO / Distribution.

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